L5: Entry 48 of 78 File: USPT Feb 15, 2000

DOCUMENT-IDENTIFIER: US 6024978 A
** See image for Certificate of Correction **
TITLE: Pharmaceutical compositions comprising cyclosporins

Brief Summary Text (6):
Since the original discovery of ciclosporin, a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes, for example, the naturally occurring cyclosporins A through Z [c.f. Traber et al. 1, Helv. Chim. Acta. 60, 1247-1255 (1977); Traber et al. 2, Helv. Chim. Acta. 65 no. 162, 1655-1667 (1982); Kobel et al., Europ. J. Applied Microbiology and Biotechnology 14, 273-240 (1982); and von Wartburg et al., Progress in Allergy, 38, 28-45 (1986)], as well as various non-natural cyclosporin derivatives and artificial or synthetic cyclosporins including the so called dihydro-cyclosporins [in which the moiety --x--y-- of the --MeBmt-- residue (Formula B above) is saturated to give --x--y--.dbd.--CH.sub.2 --CH.sub.2 --; derivatised cyclosporins (e.g. in which a further substituent is introduced at the .alpha.-carbon atom of the sarcosyl residue at the 3-position of the cyclosporin molecule); cyclosporins in which the --MeBmt-- residue is present in isomeric form (e.g. in which the configuration across positions 6' and 7' of the --MeBmt-- residue is cis rather than trans); and cyclosporins wherein variant amino acids are incorporated at specific positions within the peptide sequence, employing e.g. the total synthetic method for the production of cyclosporins developed by R. Wenger--see e.g. Traber 1, Traber 2 and Kobel loc. cit.; U.S. Pat. Nos. 4,108,985, 4,210,581 and 4,220,641; European Patent Publication Nos. 0 034 567 and 0 056 782; International Patent Publication No. WO 86/02080; Wenger 1, Transp. Proc. 15, Suppl. 1:2230 (1983); Wenger 2, Angew. Chem. Int. Ed., 24, 77 (1985); and Wenger 3, Progress in the Chemistry of Organic Natural Products 50, 123 (1986).

Brief Summary Text (189):
6.1. Solid hydrocarbons, for example petroleum jellies, e.g. white petrolatum or Vaseline.RTM., ceresin and solid paraffins, as well as waxes including animal, vegetable and synthetic axes such as, for example, spermaceti, carnauba and bees wax;

Brief Summary Text (196):
Compositions (F) may further comprise one or more consistency promoting agents, for example microcrystalline waxes, vegetable oils such as olive oils, corn oils and kernel oils, and vegetable oil derivatives including hydrogenated vegetable oils and vegetable oil partial-glycerides, e.g. in an amount of from about 0.1 to about 10%, preferably from about 1 to about 5% weight based on the total weight of the composition.

Detailed Description Paragraph Table (12):

QUANTITY 2.2. COMPONENT (mg/capsule)
Cyclosporin (e.g. Ciclosporin 50.0 (1.1)

Glycofurol 75 180.0 (2.1) Miglyol 812 90.0 (3.1.1) Cremophor RH 40 180.0 (4.6) Aerosil 200 9.0 (4.2) Methocel K100 100.0 TOTAL 609.0

L5: Entry 40 of 78 File: USPT Dec 19, 2000

DOCUMENT-IDENTIFIER: US 6162815 A
TITLE: RXR-agonist polycyclic aromatic compounds, pharmaceutical/cosmetic compositions comprising said compound and uses thereof

Brief Summary Text (9):
Briefly, the polycyclic aromatic compounds according to this invention have the following structural formula (I): ##STR3## in which R.sub.1 is a hydrogen atom, a --CH.sub.3 radical, a --CH.sub.2 --O--R.sub.3 radical, a --CH.sub.2 --O--CO--R.sub.4 radical, an --O--R.sub.5 radical, an --O--(--CH.sub.2 --)--.sub.m --(--CO--)--.sub.n --R.sub.6 radical, a --CO--R.sub.7 radical, a --CO--O--R.sub.8 radical or an --S(O).sub.p --R.sub.9 radical, wherein m, n, p and the radicals R.sub.3 to R.sub.9 are as defined below; R.sub.2 is a hydrogen atom or a halogen atom, a lower alkyl radical, an --NO.sub.2 radical, an --O--COR.sub.4 radical, an --OR.sub.9 radical or a radical ##STR4## wherein the radicals R.sub.4, R.sub.9 and R.sub.10 are as defined below; Ar is a radical selected from among those of the following formulae (a)-(e): ##STR5## X is --O--, --S(O).sub.t -- or an --NR.sub.9 -- radical wherein t is as defined below; Y and Z are each --O--, --S(O).sub.t -- or a radical --CR.sub.11 R.sub.12, wherein the radicals R.sub.11 and R.sub.12 are as defined below; m is an integer equal to 1, 2 or 3; n is an integer equal to 0 or 1; p is an integer equal to 0, 1, 2 or 3; t is an integer equal to 0, 1 or 2; R.sub.3 is a hydrogen atom or a lower alkyl radical; R.sub.4 is a lower alkyl radical; R.sub.5 is a hydrogen atom or a lower alkyl radical; R.sub.6 is a lower alkyl radical or a heterocycle; R.sub.7 is a hydrogen atom, a lower alkyl radical or a radical: ##STR6## in which R' and R", which may be identical or different, are each a hydrogen atom, a lower alkyl radical, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl radical, or an amino acid or peptide or sugar residue, with the proviso that R' and R" may together form, with the nitrogen atom from which they depend, a nitrogen-containing heterocycle; R.sub.8 is a hydrogen atom, a linear or branched alkyl radical having from 1 to 20 carbon atoms, an alkenyl radical, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl or aralkyl radical, or a sugar residue or an amino acid or peptide residue; R.sub.9 is a hydrogen atom or a lower alkyl radical; R.sub.10 is a hydrogen atom or a lower alkyl radical; R.sub.11 is a hydrogen atom or a lower alkyl radical; R.sub.12 is a hydrogen atom or a lower alkyl radical; with the proviso that Y and Z cannot at the same time each be an oxygen atom or an --S(O).sub.t -- radical.

Detailed Description Text (10):
By the term "amino acid residue" is especially intended a residue derived from lysine, glycine or aspartic acid, and by "peptide residue" is more particularly intended a dipeptide or tripeptide residue prepared via the combination of amino acids.

Detailed Description Paragraph Table (2):

(a) Ointment: (i) Compound of Example 8	0.020 g
(ii) Isopropyl myristate	81.700 g
(iii) Fluid paraffin oil	9.100 g
(iv) Silica ("Aerosil 200" marketed by DEGUSSA)	9.180 g
(b) Ointment: (i) Compound of Example 9	0.300 g
(ii) Petroleum jelly qs	100 g
(c) Nonionic water-in-oil cream: (i) Compound of Example 7	0.100 g
(ii) Mixture of emulsified lanolin alcohols, waxes and oils ("anhydrous Eucerin" marketed by BDF)	39.900 g
(iii) Methyl parahydroxybenzoate	0.075 g
(iv) Propyl parahydroxybenzoate	0.075 g
(v) Sterile	

demineralized water qs 100 g (d) Lotion: (i) Compound of Example 8 0.100 g (ii) Polyethylene glycol (PEG 400) 69.900 g (iii) Ethanol at 95% 30.000 g (e) Hydrophobic ointment: (i) Compound of Example 7 0.300 g (ii) Isopropyl myristate 36.400 g (iii) Silicone oil ("Rhodorsil 47 V 300" marketed by RHoNE-POULENC) 36.400 g (iv) Beeswax 13.600 g (v) Silicone oil ("Abil 300.000 cst" marketed by GOLDSCHMIDT) qs 100 g (f) Nonionic oil-in-water cream: (i) Compound of Example 7 0.500 g (ii) Cetyl alcohol 4.000 g (iii) Glycerol monostearate 2.500 g (iv) PEG 50 stearate 2.500 g (v) Shea butter 9.200 g (vi) Propylene glycol 2.000 g (vii) Methyl parahydroxybenzoate 0.075 g (viii) Propyl parahydroxybenzoate 0.075 g (ix) Sterile demineralized water qs 100 g _____

CLAIMS:

1. A method for treating or preventing at least one of hyperglycemia, hypertriglyceridema and hyperinsulin-emia comprising administering a therapeutically or prophylactically effective amount of a polycyclic aromatic compound having the structural formula (I) which exhibits RXR-agonistic activity: ##STR8## in which R.sub.1 is a hydrogen atom, a --CH.sub.3 radical, a --CH.sub.2 --O--R.sub.3 radical, a --CH.sub.2 --O--CO--R.sub.4 radical, an --O--R.sub.5 radical, an --O--(--CH.sub.2 --)--.sub.m --(--CO--)--.sub.n --R.sub.6 radical, a --CO--R.sub.7 radical, a --CO--O--R.sub.8 radical or an --S(O).sub.p --R.sub.9 radical, wherein m, n, p and the radicals R.sub.3 to R.sub.9 are as defined below; R.sub.2 is a hydrogen atom or a halogen atom, a lower alkyl radical, an --NO.sub.2 radical, an --O--COR.sub.4 radical, an --OR.sub.9 radical or a radical: ##STR9## wherein the radicals R.sub.4, R.sub.9 and R.sub.10 are as defined below; Ar is a radical selected from among those of the following formulae (a)-(e): ##STR10## X is --O--, --S(O).sub.t -- or an --NR.sub.9 -- radical wherein t is as defined below; Y and Z are each --O--, --S(O).sub.t -- or a radical --CR.sub.11 R.sub.12, wherein the radicals R.sub.11 and R.sub.12 are as defined below; m is an integer equal to 1, 2 or 3; n is an integer equal to 0 or 1; p is an integer equal to 0, 1, 2 or 3; t is an integer equal to 0, 1 or 2; R.sub.3 is a hydrogen atom or a lower alkyl radical; R.sub.4 is a lower alkyl radical; R.sub.5 is a hydrogen atom or a lower alkyl radical; R.sub.6 is a lower alkyl radical or a heterocycle; R.sub.7 is a hydrogen atom, a lower alkyl radical or a radical: ##STR11## in which R' and R", which may be identical or different, are each a hydrogen atom, a lower alkyl radical, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl radical, or an amino acid or peptide or sugar residue, with the proviso that R' and R" may together form, with the nitrogen atom from which they depend, a nitrogen-containing heterocycle; R.sub.8 is a hydrogen atom, a linear or branched alkyl radical having from 1 to 20 carbon atoms, an alkenyl radical, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl or aralkyl radical or a sugar residue or an amino acid or peptide residue; R.sub.9 is a hydrogen atom or a lower alkyl radical; R.sub.10 is a hydrogen atom or a lower alkyl radical; R.sub.11 is a hydrogen atom or a lower alkyl radical; R.sub.12 is a hydrogen atom or a lower alkyl radical; with the proviso that Y and Z cannot at the same time each be an oxygen atom or an --S(O).sub.t -- radical; and with the further proviso that (i) if Ar is not phenyl and R.sub.1 is --O--R.sub.5, then R.sub.5 is not a lower alkyl radical; (ii) if Ar is not phenyl and R.sub.1 is --O--(CH.sub.2)m(CO).sub.n --R.sub.6, then m is not 2 or 3; (iii) if Ar is not phenyl and R.sub.7 is --CO--R.sub.7, then R.sub.7 is not a lower alkyl radical; and (iv) if Ar is not phenyl and R.sub.1 is --S(O).sub.p --R.sub.9, then R.sub.9 is not a lower alkyl radical; or a pharmaceutically/cosmetically acceptable salt or optical or geometric isomer thereof.

17. The method of claim 1, where in the administered polycyclic aromatic compound of formula (I), the peptide residue substituents are those of a dipeptide or tripeptide.